510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
EXECUTIVE SUMMARY

A. 510(k) Number: k122397 SEP 6 2012

B. Purpose for Submission: New Device

C. Measurand: IgM Antibody to Rubella Virus

D. Type of Test: Qualitative, Chemiluminescence Immunoassay (CLIA)

E. Applicant: DiaSorin Inc.

F. Proprietary and Established Names: LIAISON® Rubella IgM
LIAISON® Control Rubella IgM

G. Regulatory Information:

1. Regulation section: 21 CFR §866.3510 Rubella Virus Serological Reagents
21 CFR §862.1660 Quality control material

2. Classification: Class II

3. Product code: LFX (Enzyme Linked Immunoabsorbent Assay, Rubella)
JJX (Quality control material, assayed and unassayed)

4. Panel: 83 Microbiology

H. Intended Use:

1. Intended use(s):

The LIAISON® Rubella IgM assay uses chemiluminescent immunoassay (CLIA) technology on the LIAISON® Analyzer for the qualitative determination of IgM antibodies to rubella virus in human serum samples. It is intended for use as an aid in the diagnosis of a current or recent Rubella infection in individuals with signs and symptoms of Rubella, or suspected of having rubella virus infection, including women of child bearing age.

The LIAISON® Control Rubella IgM (negative and positive) is intended for use as assayed quality control samples to monitor the performance of the LIAISON® Rubella IgM assay.
The performance characteristics of LIAISON® Rubella IgM controls have not been established for any other assays or instrument platforms.

2. Indication(s) for use:

Same as Intended Use.

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

LIAISON® Analyzer family of instruments is required to perform the testing.

I. Device Description:

The LIAISON® Rubella IgM assay is an *in vitro* diagnostic device consisting of reagents provided in individual compartments within a plastic container called the Reagent Integral. The assay configuration for the LIAISON® Rubella IgM assay allows for the performance of 100 tests.

Reagent Integral Composition:
a. Magnetic particles – mouse monoclonal antibody IgG to human IgM
b. Calibrator 1 - human serum or defibrinated plasma containing low level of Rubella IgM
c. Calibrator 2 - human serum or defibrinated plasma containing high level of Rubella IgM
d. Antigen - Inactivated rubella viral particles (HPV 77 strain)
c. Specimen diluent – buffer with BSA added
d. Conjugate – mouse monoclonal antibodies to rubella virus conjugated to an isoluminol derivative

The LIAISON® Control Rubella IgM is an *in vitro* diagnostic device consisting of 2 levels of controls to monitor the performance of the LIAISON® Rubella IgM assay

Controls (2 vials of each level):
Negative control - human serum or defibrinated plasma non-reactive for Rubella IgM
Positive control - human serum or defibrinated plasma reactive for Rubella IgM

J. Substantial Equivalence Information:

1. Predicate device name(s): ADVIA Centaur Rubella IgM Assay

2. Predicate 510k number(s): K010668

3. Comparison with predicate:

Table 1: Table of Similarities

Characteristic	New Device LIAISON® Rubella IgM Assay	Predicate Device ADVIA Centaur Rubella IgM (K010668)
Intended Use	The LIAISON® Rubella IgM assay uses chemiluminescent immunoassay (CLIA) technology on the LIAISON® Analyzer for the qualitative determination of IgM antibodies to rubella virus in human serum samples. It is intended for use as an aid in the diagnosis of a current or recent Rubella infection in individuals with signs and symptoms of Rubella, or suspected of having rubella infection, including women of child bearing age.	The ADVIA Centaur Rubella IgM assay is an IgM antibody capture microparticle direct chemiluminometric *in vitro* diagnostic assay for the qualitative detection of IgM antibodies to the rubella virus in serum or plasma (EDTA, heparin) as an aid in the presumptive diagnosis of current or recent infection with rubella.
Assay Type	Chemiluminescent Immunoassay	Chemiluminometric immunoassay
Measured Analyte	IgM antibodies to rubella virus	IgM antibodies to rubella virus

Table 2 : Table of Differences		
Characteristic	**New Device LIAISON® Rubella IgM Assay**	**Predicate Device ADVIA Centaur Rubella IgM (K010668)**
Sample Matrix	Serum	Serum and plasma (EDTA, heparin)

K. Standard/Guidance Document Referenced (if applicable):

CLSI: EP05-A2 Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline Second Edition 2004
CLSI: EP15-A2: User Verification of Performance for Precision and Trueness; Approved Guideline, 2006
CLSI: EP07-A2: Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition 2005

L. Test Principle:

Chemiluminescence Immunoassay (CLIA) – Immunoassay technology based on the emission of light as a result of a chemical reaction.

In the 1st incubation the IgM antibodies present in calibrators, samples or controls bind to the solid phase. During the second incubation, rubella virus antigen reacts with IgM directed against rubella virus that is already bound to the solid phase. During the third incubation, the antibody conjugate reacts with the immune complex formed during the second incubation, thus revealing that the immunological reaction has taken place. After the first and third incubations, the unbound material is removed with a wash cycle. Subsequently, the starter reagents are added and a flash chemiluminescence reaction is thus induced. The light signal, and hence the amount of isoluminol-antibody conjugate, is measured by a photomultiplier as relative light units (RLU) and is indicative of rubella virus IgM concentration present in calibrators, samples or controls.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

A twenty-day reproducibility/precision study was conducted at two external laboratories and DiaSorin Inc. The CLSI document EP5-A2 was consulted in the preparation of the testing protocol.

A coded panel was tested at all three sites, using two replicates per run in two runs per day for 20 operating days. The 20 day combined results for all 3 sites are summarized as mean AU/mL value, standard deviation, and coefficient of variation (%CV) for within run and Total across lots and across sites.

The AU/mL values for the Negative control, and 2 of the Negative precision panels gave results less than the low end of the assay range of 10 AU/mL, therefore, the RLUs were used to perform the statistical calculations for these three sample types.

Combined sites 20 day precision results

Sample ID	Mean AU/mL	Within-Run		Total (Across lots and Sites)	
		SD	%CV	SD	%CV
Negative Control*	<10*	50.1*	3.6%*	170.9*	12.3%*
Positive Control	72.5	3.0	4.2%	9.3	12.8%
Rubella IgM-A*	<10*	52.8*	3.7%*	183.3*	12.7%*
Rubella IgM-B*	<10*	115.2*	3.4%*	533.4*	15.9%*
Rubella IgM-C	19.3	0.9	4.9%	2.9	14.8%
Rubella IgM-D	23.3	1.0	4.4%	3.3	14.1%
Rubella IgM-E	33.7	1.6	4.7%	4.5	13.4%
Rubella IgM-F	115	4.8	4.1%	14.9	13.0%
Rubella IgM-G	251	9.2	3.7%	29.7	11.9%

*Dose was below the reading range of the assay. Precision calculations are based on signal (RLU) for the 3 samples.

b. Linearity/assay reportable range:

Not applicable

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Traceability:
There is no international standard available for measuring anti-Rubella IgM in serum, therefore, calibrators are traceable to an in-house reference preparation. Positive human serum/defibrinated plasma is serially diluted with negative serum/defibrinated plasma and tested in several assays and assigned Arbitrary Units (AU/mL) values spanning the range of the assay. Aliquots are stored frozen and used during the manufacturing of the kit calibrators.

Stability:
Reagent Integral
Open use stability at 2-8°C was performed on one Reagent Integral Lot. At specified intervals, the stored opened kit was evaluated in parallel with a freshly opened kit. All testing was acceptable to 9 weeks. An open use stability of 8 weeks at 2-8°C is claimed.

Open use stability on board the LIAISON® Analyzer was performed on one Reagent Integral Lot. At specified intervals, the opened kit was evaluated in parallel with a freshly opened kit. All testing was acceptable to 9 weeks. An open use stability of 8 weeks on board the LIAISON® Analyzer is claimed.

Controls
Open Use stability at 2-8°C was performed on 3 different lots of LIAISON® Control Rubella IgM. At specified intervals, the stored opened controls were evaluated in parallel with a freshly opened vial of each control. All testing was acceptable to 9 weeks. Open use stability at 2-8°C of 8 weeks is claimed.

Expected Values:
Calibrator 1 is manufactured to have a concentration between 20-35 AU/mL.
Calibrator 2 is manufactured to have a concentration between 70-250 AU/mL.

The Negative Control is manufactured to have a target range 0-12 AU/mL.
The Positive Control is manufactured to have a target range 40-110 AU/mL.

d. Detection limit:

Not applicable

e. Analytical specificity:

Cross-reactivity

The cross-reactivity study for the LIAISON® Rubella IgM assay was designed to evaluate potential interference from the presence of potentially cross-reactive antibodies or substances and other viruses that may cause symptoms similar to or that may mimic Rubella infection. Only samples that were sero-positive for the cross reactant and sero-negative for Rubella IgM by a commercially available Rubella IgM assay were used to test for potentially cross-reactive organisms.

Cross-reactive organism	Number of samples tested	Reference Rubella IgM Result	LIAISON® Rubella IgM		
			POS	EQV	NEG
IgG anti-VCA	10	Negative	0	0	10
IgM anti-EBV	10	Negative	0	0	10
IgM anti-CMV	10	Negative	0	0	10
IgG anti-VZV	10	Negative	0	0	10
IgM anti-VZV	10	Negative	0	0	10
Anti-Treponema Pallidum	10	Negative	0	0	10
IgG anti-Toxoplasma gondii	10	Negative	0	0	10
IgM anti-Toxoplasma gondii	10	Negative	0	0	10
Anti-HAV / IgM anti-HAV	10	Negative	0	0	10
Anti-HBs	10	Negative	0	0	10
IgM anti-Measles	10	Negative	0	0	10
IgM anti-Parvovirus B19	10	Negative	0	0	10
IgM anti-HSV 1/2	10	Negative	0	0	10
IgG anti-HSV 1	11	Negative	0	0	11
IgG anti-HSV 2	4	Negative	0	0	4
HHV6	10	Negative	0	0	10
ANA IgG	10	Negative	0	0	10
Chlamydia IgG	10	Negative	0	0	10
Chlamydia IgM	10	Negative	0	0	10
anti-HIV	10	Negative	0	0	10
hCG	10	Negative	0	0	10
Influenza A	7	Negative	0	0	7
Influenza B	6	Negative	0	0	6
ParaInfluenza I	8	Negative	0	0	8
ParaInfluenza II	2	Negative	0	0	2
ParaInfluenza III	6	Negative	0	0	6
anti-HCV	10	Negative	0	0	10
Rheumatoid Factor	10	Negative	0	0	10
HAMA	10	Negative	0	0	10
Multiple Myeloma	10	Negative	0	0	10
Total	261		0	0	261

High Dose Hook Effect

Analysis of high-dose hook effect was evaluated by testing three samples with rubella IgM levels out-of-range > 400 AU/mL. The samples resulted in calculated concentration values above the measuring range. There was no sample misclassification indicating no hook effect was observed.

IgM Specificity

Ten samples containing Rubella IgM antibodies covering the assay range from value around cut-off level to clearly positive samples were treated with 10 mM dithiotreitol (DTT) to denature the IgM. These DTT treated samples were then tested in singlicate in parallel with the non-treated samples. All samples showed absence of IgM anti-Rubella reactivity after treatment with DTT. These data demonstrate the specificity of the LIAISON® Rubella IgM assay for IgM immunoglobulins.

	LIAISON® Rubella IgM assay Results (AU/mL)	
Sample ID	**Before DTT treatment**	**After DTT treatment**
Sample-1	18.0	<10.0
Sample-2	17.1	<10.0
Sample-3	22.0	<10.0
Sample-4	34.7	<10.0
Sample-5	227	<10.0
Sample-6	109	<10.0
Sample-7	145	<10.0
Sample-8	86.4	<10.0
Sample-9	116	<10.0
Sample-10	148	<10.0

Interference

Testing was performed to determine whether the presence of endogenous or exogenous substances may interfere with assay results. Two matched sample pools containing antibodies to Rubella IgM near the clinical decision point were tested neat and spiked with the respective interferent. The acceptance criteria were defined as the % change in signal must not be more than +10% and no change in the qualitative result.

No interference was found at the concentration for each substance listed below in the LIAISON® Rubella IgM assay. The testing was based on CLSI-EP07-A2.

Substance	**Tested Concentration**
Triglycerides	3000 mg/dL
Hemoglobin	1000 mg/dL
Unconjugated bilirubin	20 mg/dL
Conjugated bilirubin	30 mg/dL
Albumin	6 g/dL
Cholesterol	510 mg/dL
Gamma-globulin	6000 mg/dL
L-Ascorbic acid	3 mg/dL

f. Assay cut-off:

The cutoff for the LIAISON® Rubella IgM assay was set at an Arbitrary Unit value of 25 AU/mL based on European studies by testing 1662 subjects from different populations (subjects never infected by rubella virus, subjects affected by autoimmune diseases, patients affected by various infectious diseases with similar symptomology, subjects with past rubella infector or vaccine recipients, patients affected by acute rubella infection and subjects with long–lasting rubella virus IgM). The specimens were tested by several comparison methods and the consensus between the methods as well as the available clinical and serological data were applied to define the expected results.

The assay cut-off was validated in the United States during clinical studies by testing a prospective population of 448 samples from individuals sent to the laboratory for Rubella IgM testing, and a retrospective population of 178 samples from individuals who had a positive Rubella IgM result. Based on the comparison studies this cutoff is appropriate for the LIAISON® Rubella IgM.

In the LIAISON® Rubella IgM assay, a sample is defined as positive if the Arbitrary Unit value is greater than or equal to 25 AU/mL, and defined as negative if the Arbitrary Unit value is less than 20 AU/mL. Samples with results greater than or equal to 20 AU/mL and less than 25 AU/mL are classified as equivocal.

2. Comparison studies:

a. Method comparison with predicate device:

Not applicable

b. Matrix comparison:

Not applicable

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable

b. Clinical specificity:

Not applicable

c. Other clinical supportive data (when a. and b. are not applicable):

Comparative testing

Prospective and Retrospective studies were performed to compare the performance of the LIAISON® Rubella IgM assay to an FDA-cleared predicate device.
The prospective study consisted of 448 samples from individuals who were sent to the laboratory for Rubella IgM testing.
The retrospective study consisted of 178 samples selected from individuals who had a positive Rubella IgM result.

Prospective study
The prospective population consisting of 448 individuals were 89.7% Female (n=402) ranging in age from <1 to 67 years, and 9.2% Male (n=41) ranging in age from <1 to 59 years. There were 5 samples from patients where the gender was unknown (1.1%).

The agreement with 95% Confidence intervals for the prospective population is shown in the table below.

LIAISON® Rubella IgM	Comparator Assay			Total
	Positive	Equivocal	Negative	
Positive	6	0	2	8
Equivocal	0	0	3	3
Negative	3	1	433	437
Total	9	1	438	448

		Percent Agreement	Exact 95% Confidence Interval
Negative	**433/438**	**98.9%**	**97.3 - 99.5%**
Positive	**6/10**	**60.0%**	**30.8 - 83.3%**

Retrospective study
The retrospective population consisted of 178 samples from individuals who had a positive Centaur Rubella IgM result. There were 37.1% Females (n=66) and 23% Males (n=41) ranging in age from 2 to 59. For 39.9% (n=71) of the samples, gender and age were unknown.

The agreement with 95% Confidence intervals for the pre-selected population is shown in the table below.

LIAISON® Rubella IgM	Comparator Assay			Total
	Positive	Equivocal	Negative	
Positive	175	1	0	176
Equivocal	1	0	0	1
Negative	1	0	0	1
Total	177	1	0	178

		Percent Agreement	Exact 95% Confidence Interval
Positive	**175/177**	**98.9%**	**96.0 - 99.7%**

4. Clinical cut-off:

Not applicable

5. Expected values:

The observed prevalence/ expected values using the LIAISON® Rubella IgM assay was calculated with the 448 samples from patients sent to the lab for Rubella IgM testing. The samples were from 41 males (9.2%) and 402 females (89.7%). There were 5 samples from patients where the gender was unknown (1.1%). Ages ranged from < 1 year to 67 years. There were 11 samples where age was unknown.

The prevalence may vary depending upon geographical location, age, gender, type of test employed, specimen collection and handling procedures as well as clinical history of the patient.

The observed prevalence of LIAISON® Rubella IgM is 1.8%. The results are stratified by age and gender in the following table. Three (3) equivocal results were not used in the prevalence calculation.

		Gender			LIAISON® Rubella IgM results			% Prevalence
Total	Age	Male	Female	Unknown	Pos	Eqv	Neg	
17	<1	9	6	2	1	0	16	5.9%
8	1-10	4	3	1	0	0	8	0.0%
33	11-20	6	27	0	1	0	32	3.0%
218	21-30	11	206	1	6	2	210	2.8%
137	31-40	7	130	0	0	1	136	0
14	41-50	2	12	0	0	0	14	0
8	51-60	2	6	0	0	0	8	0
2	61-70	0	2	0	0	0	2	0
11	Unknown	0	10	1	0	0	11	0

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

SEP 6 2012

DiaSorin, Inc.
C/O Carol DePouw
1951 Northwestern Avenue
Stillwater, MN 55082

Re: K122397
Trade/Device Name: LIAISON® Rubella IgM, LIAISON® Control Rubella IgM
Regulation Number: 21 CFR 866.3510
Regulation Name: Rubella Virus Serological Reagents
Regulatory Class: Class II
Product Code: LFX, JJX
Dated: August 6, 2012
Received: August 7, 2012

Dear Ms. DePouw:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket

notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Sally A. Hojvat, M.Sc., Ph.D.
Director
Division of Microbiology Devices
Office of *In Vitro* Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

510(k) Number: K122397

Device Name: LIAISON® Rubella IgM and LIAISON® Control Rubella IgM

Indication For Use:

The LIAISON® Rubella IgM assay uses chemiluminescent immunoassay (CLIA) technology on the LIAISON® Analyzer for the qualitative determination of IgM antibodies to rubella virus in human serum samples. It is intended for use as an aid in the diagnosis of a current or recent Rubella infection in individuals with signs and symptoms of Rubella, or suspected of having rubella virus infection, including women of child bearing age.

The LIAISON® Control Rubella IgM (negative and positive) is intended for use as assayed quality control samples to monitor the performance of the LIAISON® Rubella IgM assay. The performance characteristics of LIAISON® Rubella IgM controls have not been established for any other assays or instrument platforms.

Prescription Use __X__ (21 CFR Part 801 Subpart D) And/Or Over the Counter Use ____. (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) k122397